CLAIMS

What is claimed is:

1. A method of screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said method comprising:

(i) providing a mammalian cell comprising:

a nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding domain that binds said peptide binding site attached to said metabolic product or to a ligand that binds to said metabolic product; and

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product;

(ii) contacting said cell with a test agent; and

(iii) detecting an alteration of expression of said effector gene wherein a difference in the expression of said effector gene in said test cell, as compared to a control cell contacted with a lower concentration of test agent or no test agent indicates that said test agent modulates the ability of said cell to accumulate or degrade said metabolic product.

2. The method of claim 1, wherein said expression control protein is a transactivator.

3. The method of claim 2, wherein said transactivator is VP16.

4. The method of claim 1, wherein said expression control protein is a repressor.

5. The method of claim 1, wherein said nucleic acid binding protein is selected from the group consisting of GAL-4, and GAL-4-Y.

6. The method of claim 1, wherein said effector is selected from the group consisting of a reporter gene, a cytotoxin, and an apoptosis gene.

7. The method of claim 1, wherein said reporter gene is selected from the group consisting of chloramphenicol acetyl transferase (CAT), luciferase, b -galactosidase (b-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

8. The method of claim 1, wherein said effector encodes a cytotoxin selected from the group consisting of thymidine kinase, pseudomonas exotoxin, diphtheria toxin, ricin, and abrin.

9. The method of claim 1, wherein said apoptosis gene is selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

10. The method of claim 1, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its heteromelic receptor partner.

11. The method of claim 1, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

12. The method of claim 1, wherein said second chimeric protein is expressed from a nucleic acid in said cell.

13. The method of claim 1, wherein said first chimeric protein is a protein transported into said cell.

14. The method of claim 1, wherein said first chimeric protein is a protein transported into said cell.

15. The method of claim 1, wherein said first chimeric protein or said second chimeric protein comprises an HIV TAT domain.

16. The method of claim 1, wherein said cell is a cell selected from the group consisting of SW480, SW48, DLD-1, HCT-116, HT29, 293, U-20S, T-47D, MCF-7, HeLa, A549, Hep G2, and a Jarkat cell.

17. The method of claim 1, wherein

said nucleic acid encodes a GAL-4 binding site, and said effector gene is a reporter gene;

said first chimeric protein comprises a GAL-4 nucleic acid binding protein and a beta catenin or a Tcf;

said second chimeric protein comprises a VP-16 and beta catenin or a Tcf.

18. The method of claim 17, wherein said Tcf is Tcf4.

19. The method of claim 1, wherein said cell comprises a nucleic acid encoding said first or said second chimeric protein under control of a tissue specific or an inducible promoter.

20. The method of claim 19, wherein said promoter is an ecdysone promoter.

21. The method of claim 1, wherein said cell further comprises a second nucleic acid encoding said ligand or metabolic product operably linked to an inducible promoter.

22. A method of selectively expressing an effector gene in a cell that accumulates or degrades a metabolic product, said method comprising:

providing a cell comprising:

a nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding protein that binds said peptide binding site where said nucleic acid binding protein is attached to said metabolic product or to a ligand that binds to said metabolic product;

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said

metabolic product, such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product;

whereby said cell, in the absence of the ability to degrade said metabolic product or said ligand that binds said metabolic product activates or represses expression of said effector gene.

23. The method of claim 22, wherein said expression control protein is a transactivator.

24. The method of claim 23, wherein said transactivator is VP16.

25. The method of claim 22, wherein said expression control protein is a repressor.

26. The method of claim 22, wherein said nucleic acid binding protein is selected from the group consisting of GAL-4, and GAL-4-Y.

27. The method of claim 22, wherein said effector is selected from the group consisting of a reporter gene, a cytotoxin, and an apoptosis-inducing gene.

28. The method of claim 27, wherein said reporter gene is selected from the group consisting of chloramphenicol acetyl transferase (CAT), luciferase, b - galactosidase (b-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

29. The method of claim 27, wherein said effector encodes a cytotoxin selected from the group consisting of thymidine kinase, pseudomonas exotoxin, diphtheria toxin, ricin, and abrin.

30. The method of claim 27, wherein said apoptosis gene is selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

31. The method of claim 22, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its heteromelic receptor partner.

32. The method of claim 22, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

33. The method of claim 22, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

34. The method of claim 22, wherein said first chimeric protein is a protein transported into said cell.

35. The method of claim 22, wherein said first chimeric protein is a protein transported into said cell.

36. The method of claim 22, wherein said first chimeric protein or said second chimeric protein comprises an HIV TAT domain.

37. The method of claim 22, wherein

said nucleic acid encodes a GAL-4 binding site, and said effector gene is a reporter gene;

said first chimeric protein comprises a GAL-4 nucleic acid binding protein and a beta catenin or a Tcf;

said second chimeric protein comprises a VP-16 and beta catenin or a Tcf.

38. The method of claim 37, wherein said Tcf is Tcf4.

39. The method of claim 1, wherein said test agent is a small organic molecule.

40. A method of selectively killing a cell that accumulates a metabolic product, said method comprising:

transfecting said cell with a nucleic acid encoding a peptide binding site and an effector that is a cytotoxin or an apoptosis-inducing gene;

introducing into said cell a first chimeric protein comprising a nucleic acid binding protein that binds said peptide binding site where said nucleic acid binding protein is attached to said metabolic product or to a ligand that binds to said metabolic product: and

introducing into said cell a second chimeric protein comprising a transactivator attached to said metabolic product or to said ligand that binds to said metabolic product, such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product.

41. The method of claim 40, wherein said transactivator is VP16.

42. The method of claim 40, wherein said nucleic acid binding protein is selected from the group consisting of GAL-4, and GAL-4-Y.

43. The method of claim 40, wherein said effector is a cytotoxin.

44. The method of claim 43, wherein said effector is a cytotoxin selected from the group consisting of thymidine kinase, pseudomonas exotoxin, diphtheria toxin, ricin, and abrin.

45. The method of claim 40, wherein said effector is an apoptosis-inducing gene.

46. The method of claim 45, wherein effector is an apoptosis-inducing gene selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

47. The method of claim 40, wherein said ligand and metabolic product respectively are selected from the group consisting of beta-catenin and aTcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its heteromelic receptor partner..

48. The method of claim 40, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

49. The method of claim 40, wherein said first chimeric protein is expressed from a nucleic acid in said cell.

50. The method of claim 40, wherein said first chimeric protein is a protein transported into said cell.

51. The method of claim 40, wherein said first chimeric protein is a protein transported into said cell.

52. The method of claim 40, wherein said first chimeric protein or said second chimeric protein comprises an HIV TAT domain.

53. The method of claim 40, wherein said cell is a cell selected from the group consisting of SW480, SW48, DLD-1, HCT-116,HT29, 293, U-20S, T-47D, MCF-7, HeLa, A549, Hep G2, and a Jarkat cell.

54. The method of claim 40, wherein said cell is a cancer cell.

55. The method of claim 40, wherein

said nucleic acid encodes a GAL-4 binding site;

said first chimeric protein comprises a GAL-4 nucleic acid binding protein and a beta catenin or a Tcf;

said second chimeric protein comprises a VP-16 and beta catenin or a Tcf.

56. The method of claim 55, wherein said Tcf is Tcf4.

57. The method of claim 54, wherein said cancer cell is a cell from a cancer selected from the group consisting of a colorectal cancer, a lung cancer, a breast cancer, a prostate cancer, a throat cancer, a skin cancer, and an ovarian cancer.

58. A method of treatment of a cancer said method comprising the method of any one of claims 40 through 55.

59. The method of claim 62, wherein said cancer is selected from the group consisting of a colorectal cancer, a lung cancer, a breast cancer, a prostate cancer, a throat cancer, a skin cancer, and an ovarian cancer.

60. A cell comprising:

a nucleic acid encoding a peptide binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding protein that binds said peptide binding site where said nucleic acid binding protein is attached to said metabolic product or to a ligand that binds to said metabolic product; and

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product.

61. The cell of claim 60, wherein said expression control protein is a transactivator.

62. The cell of claim 60, wherein said transactivator is VP16.

63. The cell of claim 60, wherein said expression control protein is a repressor.

64. The cell of claim 60, wherein said nucleic acid binding protein is selected from the group consisting of GAL-4, and GAL-4-Y.

65. The cell of claim 60, wherein said effector is selected from the group consisting of a reporter gene, a cytotoxin, and an apoptosis-inducing gene.

66. The cell of claim 60, wherein said reporter gene is selected from the group consisting of from the group consisting of chloramphenicol acetyl transferase (CAT),

luciferase, b -galactosidase (b-gal), alkaline phosphatase, horse radish peroxidase (HRP), growth hormone (GH), and green fluorescent protein (GFP).

67. The cell of claim 60, wherein said effector encodes a cytotoxin selected from the group consisting of thymidine kinase, pseudomonas exotoxin, diphtheria toxin, ricin, and abrin.

68. The cell of claim 60, wherein said apoptosis-inducing gene is selected from the group consisting of P53, P73, Bax, Bad, FADD, and a caspase.

69. The cell of claim 60, wherein said ligand and said metabolic product respectively are selected from the group consisting of beta-catenin and a Tcf, a NF-κB and I-κB, a P53 and MDM2, a receptor and its heteromelic receptor partner.

70. The cell of claim 60, wherein said cell comprises a nucleic acid encoding said first chimeric protein.

71. The cell of claim 60, wherein said cell comprises a nucleic acid encoding said second chimeric protein.

72. The cell of claim 60, wherein said cell is a cell selected from the group consisting of SW480, SW48, DLD-1, HCT-116,HT29, 293, U-20S, T-47D, MCF-7, HeLa, A549, Hep G2, and a Jarkat cell.

73. The cell of claim 60, wherein

said nucleic acid encodes a GAL-4 binding site, and said effector gene is a reporter gene;

said first chimeric protein comprises a GAL-4 nucleic acid binding protein and a beta catenin or a Tcf;

said second chimeric protein comprises a VP-16 and beta catenin or a Tcf.

74. The cell of claim 73, wherein said Tcf is Tcf4.

75. The cell of claim 60, wherein said cell further comprises a second nucleic acid encoding said ligand or metabolic product operably linked to an inducible promoter.

76. A nucleic acid comprising a nucleic acid selected from the group consisting of

a nucleic acid encoding a chimeric protein comprising a nucleic acid binding domain attached to a Tcf4 or to a beta catanin, and

a nucleic acid encoding a transactivator attached to a beta catenin or to a Tcf4.

77. The nucleic acid of claim 76, wherein said nucleic acid comprises a nucleic acid encoding a nucleic acid binding domain attached to a Tcf4.

78. The nucleic acid of claim 76, wherein said nucleic acid comprises a nucleic acid encoding a nucleic acid binding domain attached to a beta catenin.

79. The nucleic acid of claim 76, wherein said nucleic acid comprises a nucleic acid encoding a Tcf4 attached to a transactivator.

80. The nucleic acid of claim 76, wherein said nucleic acid comprises a nucleic acid encoding a beta catenin attached to a transactivator.

81. The nucleic acid of claim 76, wherein said nucleic acid is a DNA.

82. The nucleic acid of claim 76, wherein said nucleic acid is a vector.

83. A vector comprising:

a nucleic acid encoding a peptide binding site and an effector gene;

a nucleic acid encoding a first chimeric protein comprising a nucleic acid binding protein that binds said peptide binding site where said nucleic acid binding protein is attached to said metabolic product or to a ligand that binds to said metabolic product; and

a nucleic acid encoding a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that

binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product.

84. The vector of claim 83, wherein said a nucleic acid encoding a first chimeric protein further encodes an HIV TAT domain attached to said first chimeric protein.

85. The vector of claim 83, wherein said a nucleic acid encoding a second chimeric protein further encodes an HIV TAT domain attached to said second chimeric protein.

86. A nucleic acid encoding a first chimeric protein comprising a nucleic acid binding protein that attached to a metabolic product or to a ligand that binds to a metabolic product.

87. The nucleic acid of claim 86, wherein said nucleic acid further encodes an HIV TAT domain attached to said first chimeric protein.

88. A nucleic acid encoding a second a second chimeric protein comprising an expression control protein attached to a metabolic product or to a ligand that binds to said metabolic.

89. The nucleic acid of claim 88, wherein said nucleic acid further encodes an HIV TAT domain attached to said first chimeric protein.

90. A kit for screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said kit comprising:

a container containing a mammalian cell comprising:

a nucleic acid encoding a protein binding site and an effector gene;

a first chimeric protein comprising a nucleic acid binding protein that binds said protein binding site attached to said metabolic product or to a ligand that binds to said metabolic product;

a second chimeric protein comprising an expression control protein attached to said metabolic product or to said ligand that binds to said metabolic product such that when said first chimeric protein comprises said metabolic product, said second chimeric protein comprises said ligand and when said first chimeric protein comprises said ligand, said second chimeric protein comprises said metabolic product.

91. A kit for screening for an agent that modulates the ability of a cell to accumulate or to degrade a metabolic product, said kit comprising: a container containing a nucleic acid of claim 76.

92. A kit for selectively killing a cell, said kit comprising a container containing a two-hybrid system component selected from the group consisting of:

a nucleic acid of claim 76, and

a protein encoded by a nucleic acid of claim 76.

93. A compound that modulates the ability of a cell to accumulate or to degrade a metabolic product, said compound being identified according to the method of claim 1.